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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,169	11/28/2005	Roger R. C. New	117-565	7760

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EXAMINER	
HA, JULIE	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
01/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,169	NEW, ROGER R. C.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9-14,19-24 and 26-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9-14,19-24 and 26-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 25, 2007 has been entered.

2. Claims 3-4, 8, 15-18, 25 have been cancelled and new claims 31-35 have been added. Claims 1-2, 5-7, 9-14, 19-24, 26-35 are examined on the merits in this office action.

3. Julie Ha is the Examiner of record.

Maintained Rejection

35 U.S.C. 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-2, 5-7, 9-14, 19-24, 26-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over New (US Patent # 5853748) in view of Makino et al (JP 56138168A), Modi et al (US Patent # 5653987), Desai (US Patent # 5206219) and Sonnenberg & Kotchen (Curr. Op. Neph. Hyperten., 1998, 7, 551-5).

7. New teaches a pharmaceutical composition of a macromolecular principle (insulin), a bile acid (chenodeoxycholic acid) and an additive that buffers the gut to pH 7.5-9 (sodium bicarbonate, example 4). The wherein clause in claim 1, "wherein the composition, when introduced into the intestine, does not raise the pH of the intestinal fluid above pH 7.5" is not given patentable weight, since it does not change the structure of the pharmaceutical composition. In regards to newly added claims 31-35, New teaches a composition with an enteric coating designed to prevent digestion in the stomach and to permit digestion in the small intestine (column 7, lines 37-40). The pH of the small intestine is neutral and falls within the claimed range, as evidenced by Alberts et al (Molecular Biology of the Cell, 4th ed., Chapter 22).

8. Regarding claims 24, 26, 32 and 35, New also teaches a method of enhancing the absorption of the insulin across the intestinal well in an animal body comprising administering the insulin/chenodeoxycholic acid/sodium bicarbonate composition. Regarding claims 2 and 22, the composition comprises less than 5% by weight of water (table in example 4). Regarding claim 1, the additive, sodium bicarbonate, is present at

8.3% by weight which is greater than 1% (table in example 4). Regarding claim 5, the ratio by weight of the chenodeoxycholic acid plus the additive to the insulin is 10:1 which is greater than 5:1 (table in example 4). Regarding claims 6 and 7 and 23, the composition is in the form of a solution (column 7, lines 5—55) or a solid (example 4). Regarding claims 9-11 and 19-21, the active macromolecular principle is insulin. Regarding claims 11 and 21, the composition sensitizes the subject to insulin by increasing uptake (example 4). Regarding claim 12, the non-conjugated bile acid is chenodeoxycholic acid, the acid form of chenodeoxycholate. The difference between the reference and the instant claims is that the reference does not teach propyl gallate or butyl hydroxy anisole (BHA).

9. However, Makino et al teach a pharmaceutical composition comprising an active ingredient and a bile acid, such as deoxycholic, cholic or apocholic acid, and an antioxidant such as butylhydroxytoluene, propyl gallate or lecithin each present at 10-100,000 and 10-10,000 times that of the active ingredient, respectively (abstract).

10. Desai teaches that that other adjuvants for preserving the formulation are common in pharmaceutical formulations and antioxidants like butylated hydroxyanisole, butylated hydroxytoluene, d-α-tocopherol, and propyl gallate are commonly used in pharmaceutical compositions of insulin and other protein active ingredients (column 5, lines 5-18). Typical antioxidant concentrations can be used which is usually a standard practice; these can be from 0.1% to 1.5% (w/w or w/v). Desai reference further teaches a dosage unit pharmaceutical composition, adapted for oral administration, containing as active proteinaceous ingredients erythropoietin, insulin growth hormones, calcitonin,

GCSF, cyclosporine, vasopressin or its agonists and antagonists...interferons or interleukins (column 2, lines 13-18, and Examples 1-4).

11. Modi et al teach the liquid pharmaceutical formulation adapted to oral delivery of insulin (abstract). The reference teaches that it is usual to add at least one antioxidant to prevent degradation and oxidation of pharmaceutically active ingredients (column 3, lines 33-36).

12. It would have been obvious to one of ordinary skill in the art to substitute the propyl gallate for the sodium bicarbonate in the pharmaceutical composition taught by New patent '748. The skilled artisan would have been motivated to do so given that the pKa of propyl gallate is 8.11 (CRC Handbook of Chemistry and Physics) and that New teaches that additives that buffer the gut between pH 7.5 and 9 increases the bioavailability of the insulin while limiting the toxicity of the bile acids (column 5, lines 10-18). The skilled artisan would have been further motivated by Makino et al who teaches that the bile acid and antioxidant combination renders the pharmaceutical stable to light and heat for a long period of time (abstract), Desai who teaches that antioxidants are commonly used, and Modi et al who teaches that it is usual to add at least one antioxidant to prevent degradation and oxidation of pharmaceutically active ingredient (column 3, lines 33-36). There would have been a reasonable expectation of success given that propyl gallate is commonly used in pharmaceutical compositions and has an appropriate pKa for buffering a solution between pH 7.5 and 8, and that New demonstrated that insulin and bile acids are compatible. Thus, invention as a whole was

clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

13. Regarding claims 11 and 21, it would have been further obvious to use a known insulin sensitizing agent in the pharmaceutical composition. Sonnenberg & Kotchen (Curr. Op. Neph. Hyperten., 1998, 7, 551-5) teach that troglitazone has been approved by the FDA for the treatment of type II diabetes. The skilled artisan would have been motivated to use it in the composition taught by New because Sonnenberg & Kotchen teach that troglitazone produced a significant, dose-dependent reduction in glycosylated hemoglobin and fasting glucose concentrations despite decreases in insulin doses in clinical trials involving diabetic patients (page 552). There would have been a reasonable expectation of success because the FDA has approved the use of troglitazone in combination with insulin. Therefore, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

14. Applicant argues that New teaches additives that buffer the gut between pH 7.5 and 9, and the instant application is drawn to a composition wherein the composition does not raise the pH of the intestinal fluid above pH 7.5. Therefore, the present invention cannot have been obvious in view of the cited prior art, "because it is contrary to the direct teaching of that very same prior art."

15. Applicant's arguments have been fully considered but have not been found persuasive because the cited prior arts are prima facie obvious over the instant

invention. First, Applicant seems to be implying that the rejection is based on New Patent '748 only. However, the rejection is not sorely based on the New Patent '748, but a combination of New, Makino, Modi, Desai and Sonnenberg & Kotchen references. Furthermore, the wherein clause, "wherein the composition, when introduced into the intestine, does not raise the pH of the intestinal fluid above pH 7.5" has not been given patentable weight, since the recitation does not change the structure of the pharmaceutical composition. The MPEP states the following: "Language that suggests or makes optional or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation...(C) "wherein" clauses". See MPEP 2106. Finally, New patent teaches a pharmaceutical composition comprising all of the recited components (a pharmaceutical composition of a macromolecular principle (insulin), a bile acid (chenodeoxycholic acid)), except for propyl gallate or butyl hydroxy anisole. Makino et al teach a pharmaceutical composition comprising an active ingredient and a bile acid, such as deoxycholic, cholic or apocholic acid, and an antioxidant such as butylhydroxytoluene, propyl gallate or lecithin. Additionally, Desai teaches that that other adjuvants for preserving the formulation are common in pharmaceutical formulations and antioxidants like butylated hydroxyanisole, butylated hydroxytoluene, d-a-tocopherol, and propyl gallate are commonly used in pharmaceutical compositions of insulin and other protein active ingredients. Modi et al teach the liquid pharmaceutical formulation adapted to oral delivery of insulin (abstract). The reference teaches that it is usual to add at least one antioxidant to prevent degradation and oxidation of pharmaceutically active ingredients. Since propyl gallate is compatible (in pKa) with

sodium bicarbonate, and with the additive functionality of propyl gallate in preventing degradation and oxidation and preserving the formulation, it would have been obvious for one of ordinary skill in the art to have substituted the propyl gallate for sodium bicarbonate. Since the references provide motivation, reasonable expectation of success to obtain the claimed composition, it would be a necessary property of the obvious composition not to raise the pH above 7.5 after it has introduced into the intestine.

New Objection

16. Claim 31 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 31 recites, "a method according to claim 1". However, claim 1 recites, "a pharmaceutical composition". Therefore, claim 31 is improper dependent of claim 1.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

19. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

20. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha
Patent Examiner
AU 1654

1/26/08
ANISH GUPTA
PRIMARY EXAMINER